How CBER is Using Risk Analysis to Inform Decision-making

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Risk analysis process

Use research and scientific information in quantitative analyses to inform risk management strategies

- **Estimates likelihood & magnitude of risk**
- **Evaluate and compare interventions**
- **Define data gaps and research needs**

Risk Assessment (NAS, 1983)

- Microbial and chem/toxicological framework
- A Structured Process consisting of 4 elements:
  - Hazard identification
  - Exposure assessment
  - Dose-response
  - Risk characterization
- Qualitative or Quantitative

Biologic Products

- **Blood and blood products**
  - **Whole Blood, platelets, etc.**
  - **Immune globulins**
  - **Clotting factors & thrombolytics**
- **Vaccines**
- **Tissues**
- **Monoclonal antibodies**
- **Cellular and gene therapy**

Biologics requires variety of quantitative approaches

- Blood supply modeling
- Process modeling
  - Continuum from source materials to final product
- Infectious disease modeling
  - Vaccines
- Gene-toxicological modeling
  - Dose-response

Blood Risks – Maintaining Supply & Safety

SARS, West Nile Virus, TSEs, bioterrorism agents, live vaccines (smallpox vaccine), etc.

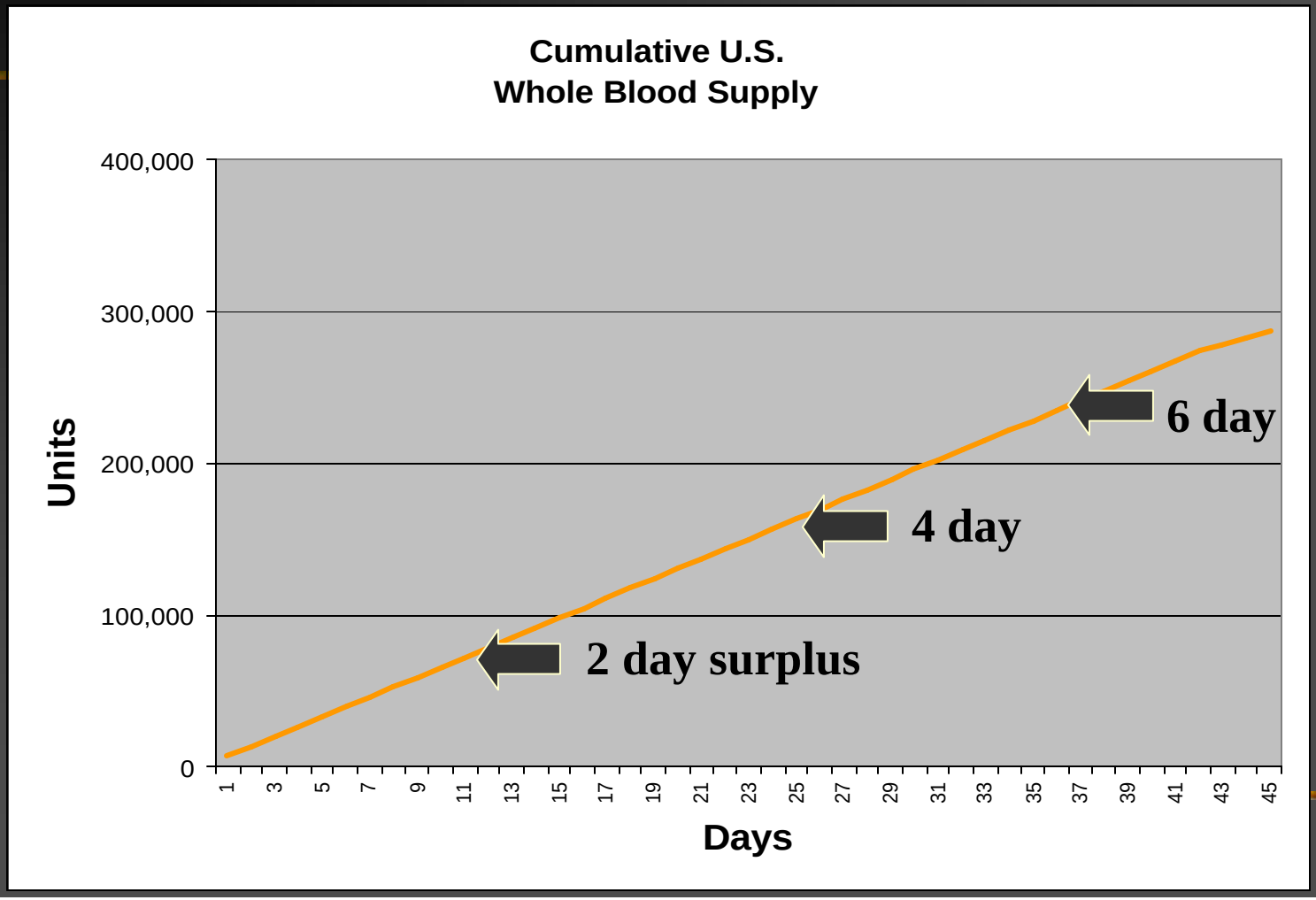
- Maintaining Adequate Supply
  - Donor Recruitment
  - Blood Utilization
  - Deferrals
- Safety of Blood Products
  - Deferrals
  - Testing
  - Processing - inactivation or removal

Whole Blood in the U.S.

- Approximately 14 million units donated / yr
- ~ 40,000 units donated / day
- ~31,000+ units utilized / day

- Approximately 5% population donate
- Store refrigerated for 42 days
- Can donate once every 56 days

US Blood Supply - model results

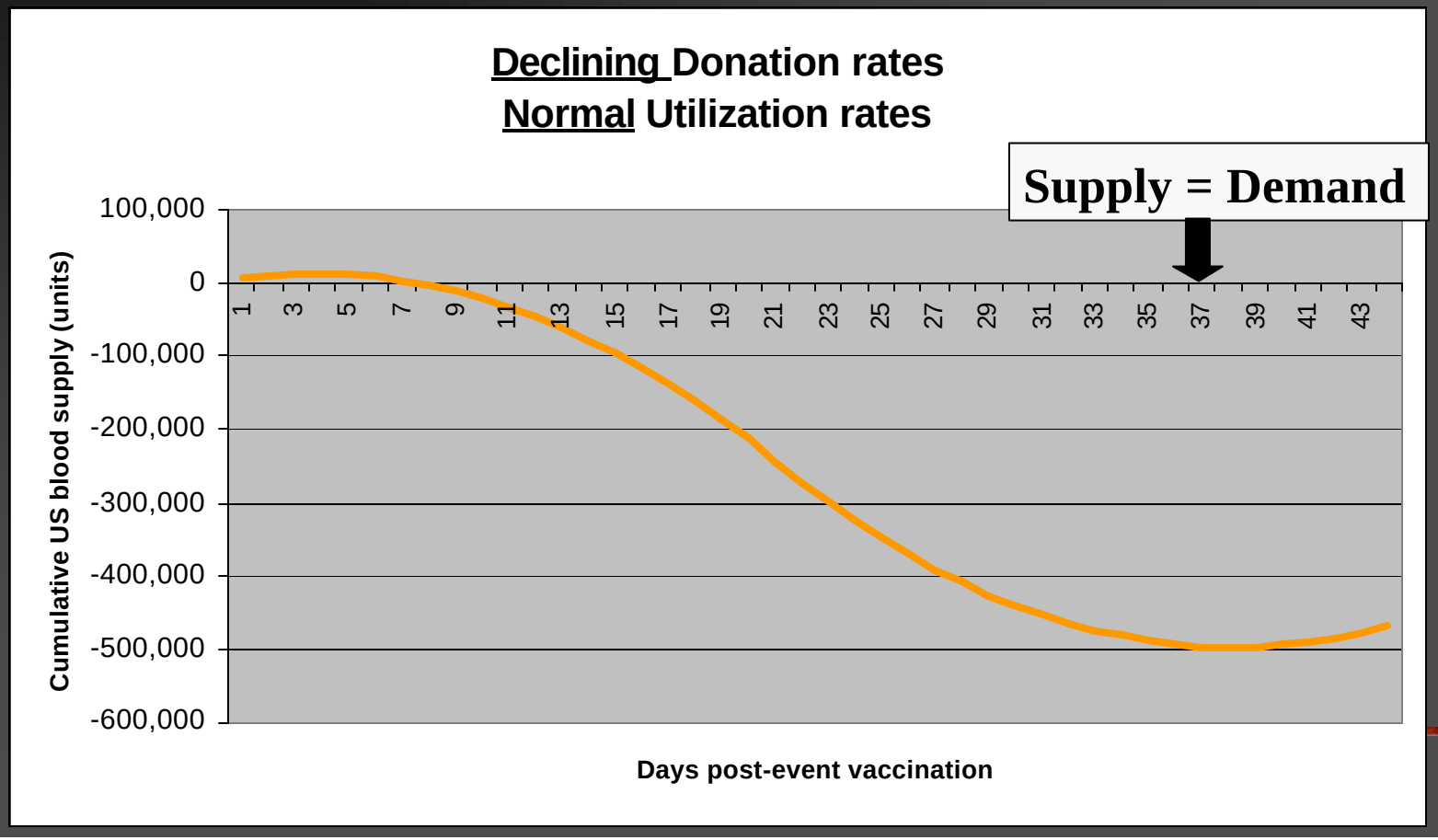


Risk Modeling of U.S. Blood Supply: Smallpox Vaccination

- **U.S. Smallpox Vaccination Program**
  - Viremia from vaccine may be a potential risk
  - 21 day vaccination deferral
- **Model impact of vaccination on blood supply**
  - Vaccinate US population in 21 days
- **Model used to evaluate interventions:**
  - 200% increase in donations
  - 50% decrease in utilization

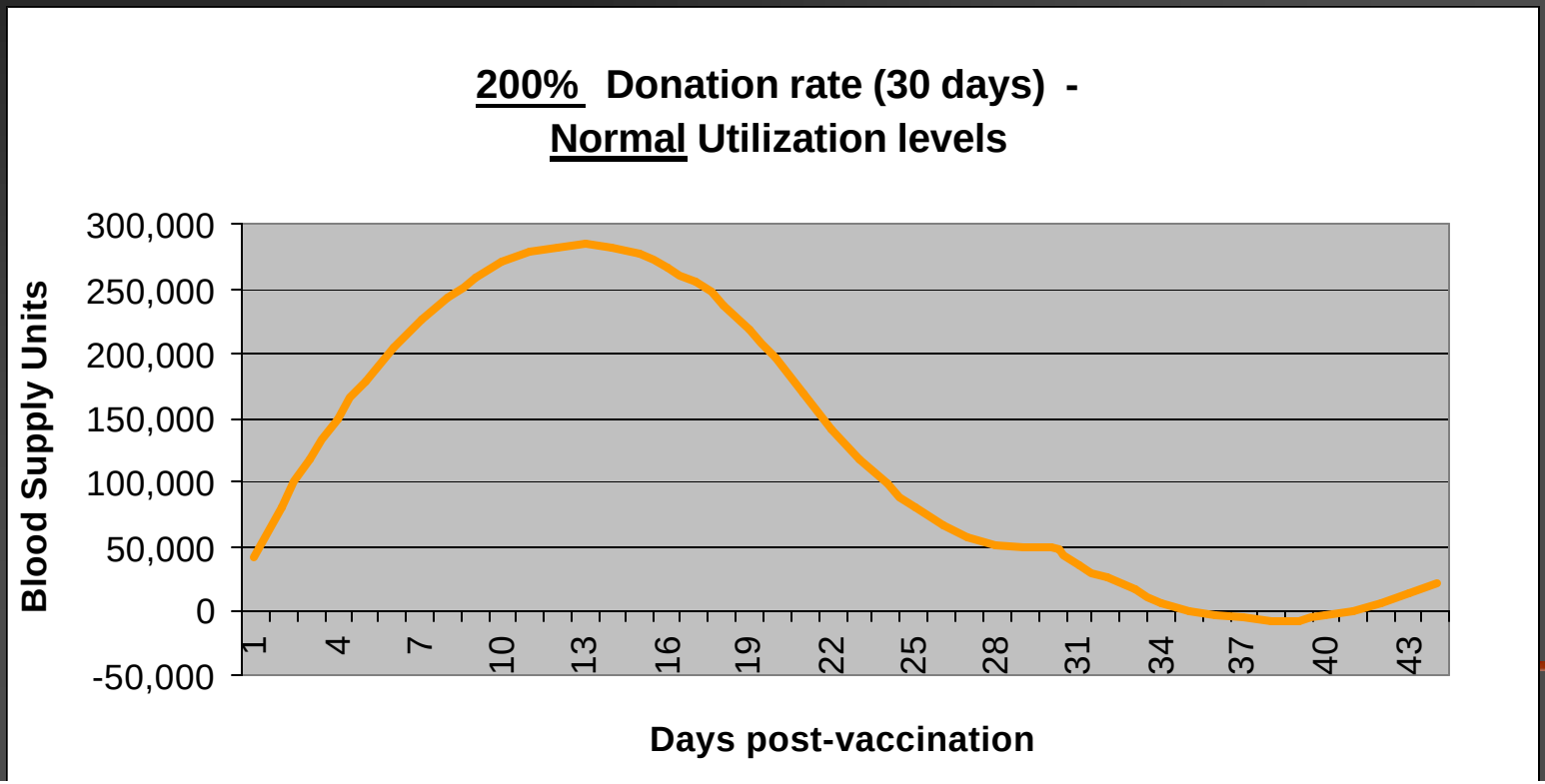
US Blood Supply & Smallpox Vaccination

21 day Campaign – U.S. Wide



Blood Supply Interventions – 200% Donation Rate

Smallpox vaccination- 21 day Campaign – U.S. Wide



Blood Supply Modeling & Smallpox vaccination

- Summary Vaccination plans:
- ≥ 21 day vaccination campaign may require 1 or a combination of interventions to maintain supply
  - 200% donation rate
  - 50% decrease in utilization
- >90 days will have little impact on the blood supply

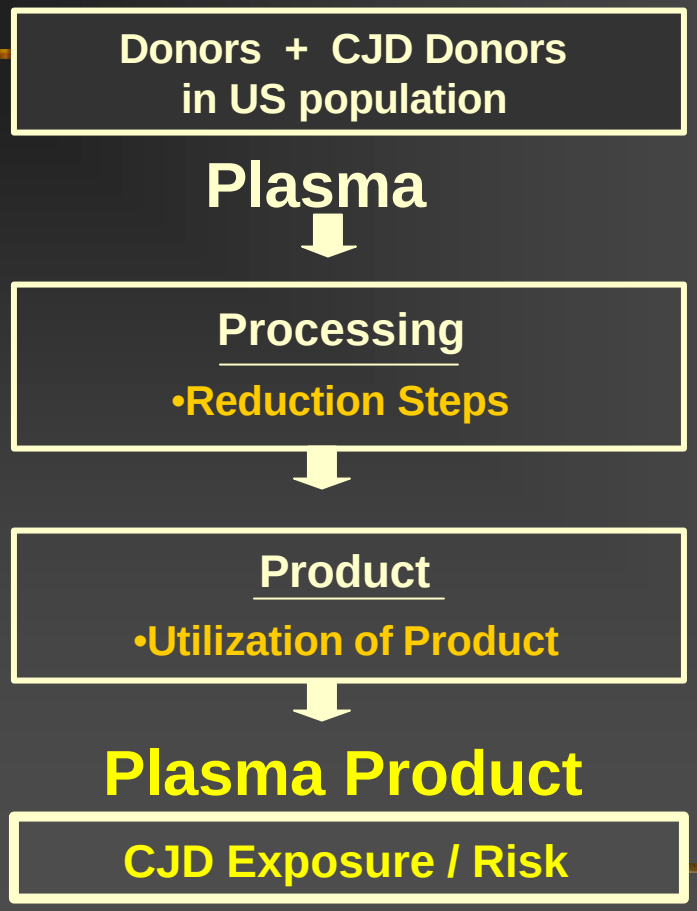
Blood Safety – CJD risks and plasma derivatives

- Creutzfeldt Jakob Disease (CJD) is a human transmissible spongiform encephalopathy (TSE)
  - Neurodegenerative disease – onset 65 yrs of age
  - Associated with prion agent
  - No rapid tests for agent & difficult to destroy
- TSE agents may be present in and transmitted via blood products
- Processing of blood plasma derivatives may reduce levels of TSEs and risk

Blood Safety – CJD risks and production of plasma derivatives

- Process models of 3 plasma derivatives to evaluate risk
  - Albumin - Burn patients, surgery
  - Immune globulins - Immune disorders
  - Factor VIII - Hemophilia A

Process Model – Plasma Derivatives



Plasma process model results

Based on SNBTS Process for fractionation (Foster et al, Vox Sang 2000)

CJD (ID_{50}*) per gram / unit basis :

Albumin (g)	**10^{-9} to 10^{-11} iv ID_{50}**
Immunoglobulins (g)	**10^{-5} to 10^{-8} iv ID_{50}**
Factor VIII (250 IU)	**10^{-4} iv ID_{50}**

*** ID_{50} – amount of agent needed to infect 50% of population**

Estimating Blood Product Risks: TSEs and Plasma Derivatives

- Models for each product were used to:
  - Estimate potential risk for each product
  - Evaluate impact of processing reduction steps on risk
- Models can be used by FDA and manufacturers to evaluate levels of risk reduction achieved by processing steps

Estimating Blood Product Risks: TSEs and Plasma Derivatives

- Models can be used by FDA and manufacturers to evaluate levels of :
  - Risk reduction achieved by processing steps
  - Risk should vCJD occur

New Initiative - Infectious Disease / Vaccine Modeling

- HIV vaccines are under development
- No HIV vaccine yet approved for marketplace
- HIV vaccines may be less effective but offer benefit

HIV Vaccine Modeling

- "What if" Modeling – can examine Implications for vaccine < 100% efficacy
  - **Will it protect?**
  - **Effect on transmission?**
  - **Changes in risk behavior?**
- Will it be accepted by at risk populations?
  - **Coverage**
- Can we explore alternative endpoints with model?
  - **Relationship decreased viral titer and lifespan**

Components
HIV Vaccine Model

- **Impact HAART therapy + vaccine**
- **Three levels of risk behavior**
  - High, medium, low
- **Type of vaccine protection**
  - Limited protection to nearly all recipients
  - High level protection to a portion of recipients

New initiative – Risk assessment retroviral gene therapy issues

- Unintended adverse events
  - Recent X-linked Severe Combined Immune Deficiency (X-SCID)
  - 2 of 9 patients treated contracted T-cell leukemia
    - Insertion into LMO-2 oncogene
  - Probably not due to chance
  - What is the probability of such insertion events?

Modeling – retroviral gene therapy

- Components of model
  - Genomic model -
    - Given a ratio of retrovirus to human cells
    - Estimate probability of insertions
    - Number of insertions per cell
  - Transformation model –
    - Probabilities for production and expansion of:
      - Beneficial clones
      - Clones leading to adverse effects
  - Goal – can interventions reduce adverse effects?
    - Adjust number of insertions, etc.
    - Use of alternate vectors?

Summary

- Models & risk assessment
- Provide important links between research & policy
  - Can address important policy questions
  - Estimate magnitude of risk
  - Model various risk management strategies
  - Identify data gaps and research priorities